REMARKS

Reexamination and reconsideration of this Application, withdrawal of the rejections, and formal notification of the allowability of all claims as now presented are earnestly solicited in light of the above claim amendments and remarks that follow.

Claims 13, 21-26, and 34 have been amended to more specifically claim the preferred embodiments of the invention. Particularly, claims 13, 21, 26, and 34 have been amended such that the Markush recitation is in alternate and singular form. Claims 13 and 21 have also been amended to remove alkyl as an option for R_1 when X_3 is NR_1. Applicant respectfully submits no new matter has been added by the present amendments. Claim 17 has been cancelled without prejudice or disclaimer, and Applicant reserves the right to file continuing applications to claim the cancelled subject matter. Accordingly, claims 13-16 and 18-38 are pending in the present application.

Claims 13-38 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. In particular, the Office argues the use of the phrase "and pharmaceutically acceptable salts thereof" in claims 13, 21, 26, and 34 renders the claims indefinite. Claims 13, 21, 26, and 34 have each been amended to recite "or a pharmaceutically acceptable salt thereof." Accordingly, Applicant respectfully submits the rejection has been obviated.

The Office further argues that recitation of the phrase "carboxylic acid, carboxylic ester, carboxamide" in claims 13, 21, 26, and 34 in definition of X_1 and X_2 renders the claims indefinite. Applicant respectfully submits the Office has mischaracterized the language of the claims.

Claims 13 and 26 (and their dependent claims 21 and 34, respectively) recite a compound according to the specified formula wherein one of X_1 and X_2 is nitrogen and the other is carbon. The claims further recite that each carbon atom of the heteroaryl rings is optionally substituted with a substituent selected from the group that includes (among other substituents) carboxylic acid, carboxylic ester, and carboxamide. In other words, the phrase "carboxylic acid, carboxylic ester, carboxamide" defines possible substituents for each carbon atom of the heteroaryl rings, and does not define X_1 and X_2. Applicant further respectfully submits that the scope of the term carboxylic acid is clear as it is readily recognizable by one of skill in the art as referring to a

group including the functional component C(O)-OH. Accordingly, Applicant respectfully submits the noted claim language is not indefinite, and Applicant requests reconsideration and withdrawal of the rejection.

Claims 26-34 stand rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. Specifically, the Office admits the specification is enabling for treating breast cancer and human melanoma, but the Office argues the specification does not reasonably provide enablement for treating any or all cancer. For multiple reasons outlined below, Applicant respectfully traverses this rejection.

Initially, Applicant respectfully directs the attention of the Office to Examples 32 through 36 of the present application, which describe the effects of the compounds of the invention for a wide variety of human cancer cell lines. In particular, the cited examples illustrate that multiple compounds of the invention are effective for inhibiting VEGF production and TF production in human melanoma cells, human prostate cancer cells, and human breast cancer cells. Further, Example 38 of the application describes testing of the compounds of the invention on 60 human tumor cell lines using the National Cancer Institute (NCI) Anti-Tumor Screen to determine median growth inhibitory concentration and median lethal concentration. Specifically, the example illustrates useful anti-cancer properties for compounds of the invention in relation to leukemia, non-small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer. This breadth of activity of the compounds of the invention, as shown in these examples, clearly supports the scope of the present claim language.

Applicant further directs the attention of the Office to Adams, Ferstl, *et al.* (Synthesis and Biological Evaluation of Novel Curcumin Analogs as Anti-Cancer and Anti-Angiogenesis Agents, *Bioorganic & Medicinal Chemistry*, 12 (2004) 3871-3883), and Adams, Cai, *et al.* (EF24, a Novel Synthetic Curcumin Analog, Induces Apoptosis in Cancer Cells Via a Redox-Dependent Mechanism, *Anti-Cancer Drugs* 2005, 16:263-275), which are provided herewith. Adams, Ferstl *et al.* disclose broad anti-cancer and anti-angiogenesis action exhibited by curcumin analogs, such as those disclosed in the present application. In particular, at page 3877, Adams, Ferstl *et al.* disclose that symmetrical α,ß-unsaturated ketones structures, such as those

described in the present application, show increased in vitro anti-cancer and anti-angiogenesis activity compared to the ß-diketone structure of curcumin.

Adams, Cai, *et al.* similarly disclose compounds, such as described in the present application, as exhibiting the following functions: induction of cell cycle arrest and apoptosis in breast cancer and human prostate cancer cells; promoting depolarization of mitochondrial membrane potential; and reduction of intracellular GSH in cancer cells. Such effects provide further support indicating the present claims are properly supported by the specification.

Next, Applicant respectfully submits the Office is incorrectly relying on Chen *et al.* (Thromb. Haemost. 86(1): 334-345, 2001) to argue the state of the art indicates undue experimentation would be required to practice the presently claimed method of treating cancerous tissue. In particular, the Office alleges Chen *et al.* teaches VEGF/TF inhibition activity effects are unpredictable and are still exploratory. Applicant, however, respectfully submits the Office has mischaracterized Chen *et al.* and has failed to appreciate the true teaching provided therein. To assist the Examiner, Applicant has provided a full text copy of Chen *et al.*

Chen *et al.* broadly state in their opening paragraph that TF serves as a regulator of angiogenesis, tumor growth, and metastasis. More specifically, at page 336, Chen *et al.* disclose that TF is associated with enhanced *in vivo* growth of a variety of primary tumor cells. They further disclose at page 336 that clinical data suggest a relation between TF and tumor angiogenesis, and that a correlation between TF and VEGF has been described in various human tumors (citing three separate sources). Still further, they note that VEGF was discovered in patients with non-small-cell carcinoma and is supposed to serve as a prognostic and predictive factor. Therefore, contrary to the Office's assertion, Chen *et al.* actually teach that TF and VEGF are very good predictors of cancerous activity.

MPEP 2164.01 states the test of enablement is not whether any experimentation is necessary, but whether any necessary experimentation is undue. Further, MPEP 2164.06 states a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. In light of these standards, Applicant respectfully submits that claims 26-34 are fully enabled by the present specification.

As pointed out above, the state of the art clearly supports VEGF and TF inhibition as a reliable indicator of anti-cancer activity. Page 16, lines 10-23, of the present specification states that, for purposes of cancer therapy, a compound of the invention is administered to the subject in an amount sufficient to inhibit production of TF or VEGF, thereby inhibiting angiogenesis. The specification further provides guidelines for dosing and treatment duration. As previously noted, Examples 32-38 of the specification illustrate inhibition of VEGF production and TF production in human melanoma cells, human prostate cancer cells, and human breast cancer cells. The Examples further describe testing on 60 human tumor cell lines and illustrate anti-cancer effects for leukemia, non-small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer.

Accordingly, as set forth in MPEP 2164.06, the present specification provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to determine effectiveness of the invention in treating further types of cancerous tissue. Moreover, one of skill in the art would need only perform routine assays (also described in the specification) to make a determination of the presence of TF or VEGF activity and to determine efficacy of treatment of a specific type of cancerous tissue. Still further, the availability of the standard NCI Anti-Tumor Screen, such as described in the specification, indicates that routine testing for anti-cancer effects is well within the level of skill in the art. Therefore, Applicant respectfully submits one of skill in the art would not be required to perform undue experimentation to practice the claimed invention in light of the present specification as the specification provides evidence of a reasonable expectation of anti-cancer efficacy generally and provides detailed direction for performing simple assays to determine efficacy in specific cases.

Finally, in relation to the rejection of claims 26-34, applicant respectfully points out that claims of similar breadth were allowed in the parent application of which the present application is a continuation. Accordingly, in light of the above several arguments, Applicant respectfully submits the cited claims are fully enabled by the specification, and Applicant requests reconsideration and withdrawal of the rejection.

Claims 13-15, 19-20, 22-23, 25-28, 30, 32-33, and 38 stand rejected under 35 U.S.C. §102(b) as being anticipated by El-Subbagh *et al.*, J. Med. Chem. 43: 2915-2921, 2000.

Applicant respectfully submits that El-Subbagh *et al.* have been incorrectly cited as a prior art reference under §102(b). The present invention is a continuation of U.S. Patent Application Serial No. 09/729,662, filed December 4, 2000. The earliest publication date provided for El-Subbagh *et al.* is July 7, 2000, which is less than one year prior to the effective filing date of the present application. Accordingly, Applicant respectfully submits that El-Subbagh *et al.* should be removed as a reference under §102(b).

Although Applicant submits El-Subbagh *et al.* has been incorrectly applied, Applicant wishes to make the following observations about the reference. The Office argues El-Subbagh *et al.* teach several compounds, compositions, and methods of use as presently claimed, particularly pointing to compound 13, which discloses 1-methyl-3,5-bis-(4-pyridylidene-4-piperidone). As presently amended, claims 13-15, 19-20, 22-23, and 25 do not encompass compounds having a central piperidone ring that is N-substituted with a methyl group. Further, compound 13 is described solely as possessing activity against HIV-1 cytopathic effect, and there is no indication in El-Subbagh *et al.* that compound 13 is useful for treating cancerous tissue, as recited in claims 26-28, 30, 32-33, and 38. The absence of anti-cancer activity for compound 13 is further illustrated in that El-Subbagh *et al.* failed to include compound 13 in the anti-tumor testing reported in Tables 3 and 4 of the reference. Therefore, Applicant respectfully submits that, even if properly cited as a reference against the noted claims, El-Subbagh *et al.* would not anticipate the presently amended claims.

Claims 13, 17-18, and 20 stand rejected under 35 U.S.C. §102(b) as being anticipated by Desiraju *et al.*, Indian Journal of Chemistry, 27B(10): 953-954, 1988 (Abstract). Desiraju *et al.* disclose the compound 2,5-bis(2-pyridinylmethylene) cyclopentanone. Claim 17 has been cancelled. As presently amended, claims 13, 18, and 20 do not encompass compounds wherein the central ring group is a cyclopentanone group. Accordingly, Applicant respectfully submits the cited claims are not anticipated by Desiraju *et al.*, and Applicant requests reconsideration and withdrawal of this rejection.

Claims 13, 17-18, and 20 stand rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 3,515,559. The '559 patent discloses compounds having cyclohexanone as the central ring group. Claim 17 has been cancelled. As presently amended, claims 13, 18, and 20

do not encompass compounds wherein the central ring group is a cyclohexanone group. Accordingly, Applicant respectfully submits the cited claims are not anticipated by the '559 patent, and Applicant requests reconsideration and withdrawal of this rejection.

Claims 13-15 and 18-25 stand rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 3,852,279. In support of the rejection, the Office particularly points to Example 13, which discloses the intermediate compound 1-methyl-3,5-bis-(2-pyridylidene)-4-piperidone. As presently amended, claims 13-15 and 18-25 do not encompass compounds having a central piperidone ring that is N-substituted with a methyl group. Accordingly, Applicant respectfully submits the cited claims are not anticipated by the '279 patent, and Applicant requests reconsideration and withdrawal of this rejection.

In further relation to claims 23-25, which are directed to pharmaceutical formulations, Applicant respectfully submits the '279 patent has been improperly applied. The compound disclosed in Example 13 of the '279 patent is an intermediate in the preparation of the pyrazolo pyridine compound that is the subject of the example. The '279 patent, however, provides no teaching or suggestion that the intermediate compound itself possesses any specific pharmaceutical activity. Accordingly, Applicant respectfully submits the '279 patent is not available as a reference against these claims.

Claims 13, 17-18 and 20 stand rejected under 35 U.S.C. §102(b) as being anticipated by Katritzky *et al.*, Journal of Heterocyclic Chemistry 25(5), 1321-1325 (Abstract). Katritzky *et al.* disclose compounds having cyclopentanone or cyclohexanone as the central ring group. Claim 17 has been cancelled. As presently amended, claims 13, 18, and 20 do not encompass compounds wherein the central ring group is a cyclopentanone or cyclohexanone group. Accordingly, Applicant respectfully submits the cited claims are not anticipated by Katritsky *et al.*, and Applicant requests reconsideration and withdrawal of this rejection.

Claims 13-15 and 19-20 stand rejected under 35 U.S.C. §102(b) as being anticipated by Gutkowska, Akad. Poloniae Pharmaceutica, 30(4), 361-364, 1973 (Abstract). Gutkowska discloses a 1-butyl-3,5-bis-(4-pyridylidene-4-piperidone) trihydrochloride salt. As presently amended, claims 13-15 and 19-20 do not encompass compounds having a central piperidone ring that is N-substituted with a butyl group. Accordingly, Applicant respectfully submits the cited

claims are not anticipated by Gutkowska, and Applicant requests reconsideration and withdrawal of the rejection.

Applicant respectfully submits that all claims, as now submitted, are in condition for immediate allowance. Accordingly, a Notice of Allowance is respectfully requested in due course. If any minor formalities need to be addressed, the Examiner is directed to contact the undersigned attorney by telephone to facilitate prosecution of this case.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR §1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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